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Generalized Necessary and Sufficient Conditions for Annihilation of HIV-1 Virions During HAART

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Abstract: In this paper, the patho-physiological dynamics of Human Immuno-deficiency Virus type 1(HIV-1) induced AIDS during Highly Active Anti Retroviral Therapy (HAART) is modeled by a system of non-linear deterministic differential equations. The physiologically relevant and clinically plausible equations depict the dynamics of uninfected $CD4^+$ T cells (x_1), HIV-1 infected CD4+ T cells (x_2), HIV-1 virions in the blood plasma (x_3), HIV-1 specific $CD8^+$ T cells (x_4), and the concentration of HAART drug molecules (x_5). Criteria for the existence of therapeutic outcomes are presented. In particular, the necessary and sufficient conditions for the annihilation of HIV-1 virions, and HIV-1 infected helper T cells are clearly exhibited in terms of biological measureable model physiological parameters. Investigative computer simulations are presented elucidating the patho-physiodynamics of HIV-1 induced AIDS and various hypothetical patient parametric configurations. The mathematical analysis of the model equations and the computer simulations are performed with regard to HAART protocols with constant continuous intravenous and transdermal drug infusions.

Keywords: HIV-1patho-physiodynamics, mathematical modeling, HAART therapy, AIDS cure criteria, Michaelis-Menten kinetics

AMS Subject Classification: 93A30; 93D05; 93D20; 34A34; 92C42; 92C35

1. Introduction

Highly Active Anti-retroviral Therapy (HAART) is currently the most therapeutically efficacious treatment protocol for treating the Acquired Immunodeficiency Syndrome (AIDS). HIV-1 virions induce AIDS by orchestrating an irreversible destruction of the $CD4^+$ T cells which then paralyze the immune system of the HIV-1 positive person. The major objectives of HAART therapy are the prolongation and improvement of the long-term life quality of patients; optimization of therapy such as to suppress the HIV-1 viral load to below 50 copies of HIV-1 RNA; reconstitution of the patients' immune system such that the CD4+ T cells proliferate to carrying capacity; and minimization of drug toxicity. HAART treatment protocol consists of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, anti-fungals /anti-bacterials and in future, integrase inhibitors. The reverse transcriptase inhibitors prevent reverse transcription of HIV-1 specific DNA. The protease inhibitors are antagonistic to maturation and formation of new HIV-1 virions. The possible role of integrase inhibitors is to prevent the integration of HIV-1 viral DNA into the patients' DNA[5,12] .

In order to achieve the therapeutic goals of HAART, it is plausible to involve the techniques of mathematical modeling. Before the advent of HAART, the primary focus of the mathematical modelers is to quantitatively analyze the observed patho-physio dynamics of HIV-1 infection in the AIDS patients. These earlier research papers involve the pioneering work of Perelson et al. [13], Nowark et al [11], and other contributors [16,17].

A recent paper by Nani and Jin [10] provided some physiological criteria under which HIV-1 virions in an AIDS patient can be annihilated during HAART.

Some of the earlier mathematical modeling publications focus on single-drug AIDS therapy using Zidovudine (INN) or azidothymidine (AZT) [9]. Then the advent of Active Retro-viral Therapy (ART) and the associated clinical limitation let to the development of HAART treatment protocols. In spite of the initial success of HAART, there are clinically measurable and observable shortcomings in the treatment of AIDS [4,]. In particular, HAART is not successful in about 40% of AIDS patients because of drug-induced toxicity and complications of treatment . HAART protocols have been clinically observed to have limited therapeutic efficacy due to biochemical/clinical drug resistance, short drug half-life, low bio-availability and blood plasma toxicities.

Mathematical modeling provides a quantitative and rational approach to solve the therapeutic efficacy problems associated with HAART. In particular, the models focused on finding optimal therapeutic schedules, the roles of latent viral reservoirs as well as minimizing of toxic side effect[1,2,6,7,8,9,14,16,17].

Optimal therapies that will minimize side effects have been investigated by many authors in [8, 9, 10, 11, 13, 14, 15, 16]. Zaric et al. in 1998 presented a model which was focused on the simulation of protease inhibitors and role of drug resistant HIV-1 virions [18]. Stengel in [14] presented a mathematical model of HIV-1 infection and HAART which demonstrated the efficacy of a mathematically optimal therapy. Caetano and Yoneyama in [2] constructed a HAART model which incorporated the roles of latently infected $CD4^+$ T cells, and discussed how the reverse transcriptase and protease inhibitors affected HIV-1 dynamics during HAART, using the LQR, Scheme. In a future paper, we will use Pontryagin's Minimal Principle to construct admissible optimal therapies such as to minimize the toxicity of the drug but maximize the therapeutic efficacy of HAART.

In this paper, an elaborate mathematical model will be constructed which will incorporate physiologically plausible effects such as Michaelis-Menten kinetics, role of HIV-1 latent viral reservoirs, continuous transdermal drug delivery, and the implicit lymphocyte proliferation induction by the $CD4^+$ T cells. The activation and proliferation is accomplished by a paracrine and autocrine processes which are mediated by the cytokine interleukin-2, secreted by the $CD4^+$ T cells. Several authors investigated the consequences of structured long-term and short-term treatment interruptions during HAART [1, 2, 4, 8]. The current model will discuss these consequences by means of simulations.

The current paper will be divided into seven sections. The first section gives the introduction into HAART therapy and provides the basis for current research. This is followed by presentation and discussion of the model parameters in Section 2. In Section 3 the mathematical model of HAART therapy will be constructed. Also the necessary and sufficient criteria for annihilation of HIV-1 virions during HAART will be presented in sections 4, 5, and 6. In Section 7, clinically plausible computer simulations will be exhibited. Section 5 will be the summary and discussion of the basic results of the paper.

2. Parameters

In this section, the physiological variable and parameters of the HAART model equations will be defined and explained. It must be emphasized that some of these parameters are biologically measurable or can be estimated using clinical techniques. In clinical experience, these parameters are different from patient to patient depending on their patho-physiological conditions.

A list of model parameters, constants, and variables is shown as follows.

x_1: the number density of non-HIV-1-infected $CD4^+$ helper T-lymphocytes per unit volume

x_2: the number density of HIV-1 infected $CD4^+$ helper T-lymphocytes per unit volume

x_3: the number density of HIV-1 virions in the blood plasma per unit volume

x_4: the number density of HIV-1 specific $CD8^+$ cytotoxic T-lymphocytes per unit volume

x_5: the concentration of drug molecules of the HAART treatment protocol

S_1: rate of supply of un-infected $CD4^+$ T_4-lymphocytes

S_2: rate of supply of latently infected $CD4^+$ T_4-lymphocytes

S_3: rate of supply of HIV-1 virions from macrophage, monocytes, microglial cells and other lymphoid tissue different from T_4-lymphocytes

S_4: rate of supply of $CD8^+$ T_8 lymphocytes from the thymus

D: rate of HAART drug infusion by transdermal delivery

a_i, b_i: constant associated with activation of lymphocytes by cytokine interleukin-2 (IL-2) (i =1, 2, 3, 4)

c: rate of HAART drug degradation and excretion

α_i: constant associated with HIV-1 infection of $CD4^+$ T_4 helper cells (i =1, 2, 3)

β_1: the number of HIV-1 virions produced per day by replication and budding in $CD4^+$ T_4 helper cells

β_2: rate constant associated with replication and "budding" of HIV-1 in syncytia $CD4^+$ T_4 helper cells per day per microliter (μl) and released into the blood plasma

β_3: the number of HIV-1 virions produced per day by replication and "budding" in non-syncytia $CD4^+$ T_4 helper cells and released into the blood plasma

η_i: constant depicting the rate of which HIV-1 virions incapacitate the $CD8^+$ T_8 cytotoxic cells (i =1, 2)

(σ_0, λ_0): Michaelis-Menten nonlinear metabolic rate constants associated with HAART drug elimination

(σ_i, λ_i): Michaelis-Menten nonlinear metabolic rate constants associated with HAART drug pharmacokinetics (i =2, 3)

ξ_i: cytotoxic coefficient where $0 \le \xi_i \le 1$ ($i = 2, 3$)

q_i: constant depicting competition between infected and un-infected $CD4^+$ T_4 helper cells ($i = 1, 2$)

k_i: constant depicting degradation, loss of clonogenicity or "death" ($i = 1, 2, 3, 4$)

k_5: rate constant depicting linear drug elimination pharmacokinetics

e_{i0}: constant depicting death or degradation or removal by apoptosis (programmed cell death) ($i = 1, 2, 3, 4$)

K_i: constant associated with the killing rate of infected $CD4^+$ T_4 cells by $CD8^+$ T_8 cytotoxic lymphocytes ($i = 1, 2$)

All the parameters are positive

3. Model Equations

3.1. Description of the Model Equations

The HIV-1 patho-physiological dynamics during HAART therapy can be modeled using the following system of non-linear ordinary differential equations:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - \alpha_1 x_1 x_3 - q_1 x_1 x_2 - k_1 x_1 - e_{10} \\ \dot{x}_2 = S_2 + a_2 x_1 x_2 e^{-b_2 x_1} + \alpha_2 x_1 x_3 - q_2 x_1 x_2 - k_2 x_2 - \beta_1 x_3 \\ \qquad - K_1 x_2 x_4 - e_{20} - \dfrac{\xi_2 \sigma_2 x_2 x_5}{\lambda_2 + x_5} \\ \dot{x}_3 = S_3 + \beta_2 x_2 x_3 + \beta_3 x_3 - \alpha_3 x_1 x_3 - \eta_1 x_3 x_4 - k_3 x_3 - e_{30} \\ \qquad - \dfrac{\xi_3 \sigma_3 x_3 x_5}{\lambda_3 + x_5} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - K_2 x_2 x_4 - \eta_2 x_3 x_4 - k_4 x_4 - e_{40} \\ \dot{x}_5 = Df(t) - \dfrac{\sigma_0 x_5}{\lambda_0 + x_5} - \dfrac{\sigma_2 x_2 x_5}{\lambda_2 + x_5} - \dfrac{\sigma_3 x_3 x_5}{\lambda_3 + x_5} - k_5 x_5 \\ f(t) = \begin{cases} 1 & \text{for constant continuous input} \\ \left| \lceil \sin nt \rceil \right| & \text{for periodic input} \end{cases} \\ x_i(t_0) = x_{i0} \quad for \quad i = \{1, 2, 3, 4, 5\} \end{cases} \tag{3.1}$$

The model includes the following clinical improvements:

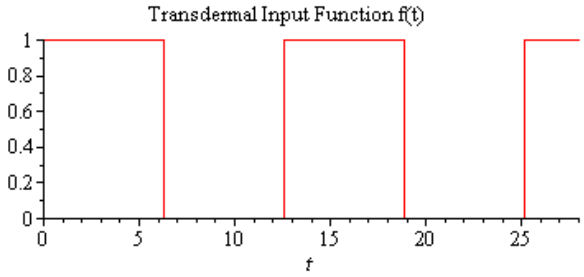
(i) The drug delivery uses transdermal, stealth-liposome encapsulated drug delivery, instead of the matrix tablet form because of improved therapeutic efficacy and reduced gastro-intestinal toxicity [6]. It is also assumed that elastic liposomes are formulated and selectively targeted such as to reduce toxicity to non-HIV-1-infected $CD4^+$ T cells (x_1) and $CD8^+$ cytotoxic T cells (x_4).

(ii) The HAART drug is such that each renal excretion and body clearance rate follows Michaelis-Menten kinetics.

(iii) $g(x_1, x_j) = a_j x_1 x_j e^{-b_j x_1}$ for j=(1, 2, 4)

This function depicts the process of lymphocyte activation which is mediated by x_1 (CD 4^+) T helper cells. These cells secrete a cytokine called interleukin-2.

(iv) The periodic input function $f(t) = |\text{ceil}(\sin(5t))|$ can be depicted by the following plot:



3.2. Boundedness and Invariance of Non-negativity of Solutions

In this subsection theoretical conditions will be constructed under which solutions to the HAART mathematical model equations are well-posed, ultimately bounded, and exhibit invariance of non-negativity for all $t \in [t_0, T] \subset \Re_+ = [0, \infty)$. In this case, t_0, and T are defined respectively as times at which HAART therapy begins and terminates.

Theorem 3.1 Consider

(i) $$\Omega = \left\{ (x_1, x_2, x_3, x_4, x_5) \in \Re_+^5 \,\middle|\, 0 \le x_i \le \Phi_i \; i = 1\ , 2, 3, 4, 5 \right\}$$

$$where \quad \Phi_i = \sup_{t \in [t_0, T]} x_i$$

Let

$$\Phi_i = \max \left\{ (x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i}),\ i = 1, 2, 3, 4 \right\}$$

(ii)

$$\Phi_5 = \max\{\ x_{50}, \frac{D}{\delta}\}$$

Then there exists a $T_0>0$ such that for $T_0 < t < \infty$, all solutions to the HAART model equations (3.1) with initial values $x_{i0} \in \Re^5_+ = \{x_i \in \Re \mid x_i \ge 0,\ i=(1,2,3,4,5)\}$ are ultimately bounded, dissipative, and will eventually enter the non-negatively invariant region Ω. In particular, the solutions are trapped in the region Ω for all $t > T_0 \subset \Re_+$

Proof. Using the result from Nani and Jin in [10], let

$$\begin{aligned} C_j &= \sup_{t \in [t_0, T]} \left[a_j x_1 x_j e^{-b_j x_1} \right] \quad for\ j = \{1,2,4\} \\ C_3 &= \sup_{t \in [t_0, T]} \left[\beta_2 x_2 x_3 + \beta_3 x_3 \right] \end{aligned} \tag{3.2}$$

Define

$$\delta_i = \sup_{t \in [t_0, T]} \left[\frac{1}{\lambda_i + x_5} \right] \quad for\ i = \{0,2,3\} \tag{3.3}$$

And set

$$\delta = \delta_0 + \delta_2 + \delta_3 \tag{3.4}$$

The Kamke comparison theorem , cf. [10] can be used to establish the following inequalities.

$$\begin{cases} x_i \le \dfrac{S_i + C_i - e_{i0}}{k_i} + \gamma_i e^{-k_i t} \quad for\ \ i = \{1,2,34\} \\ x_5 \le \dfrac{D}{\delta} + \gamma_5 e^{-\delta t} \quad where \quad \delta = \delta_0 + \delta_2 + \delta_3 \\ \quad and\ \ \gamma_i \in R_+ = (0, \infty)\ and\ \ i = \{1,2,3,4,5\} \end{cases} \tag{3.5}$$

In particular, the following results can be obtained.

$$\limsup\ x_t(t) \le \frac{S_i + C_i - e_{i0}}{k_i}, \quad i = \{1,2,3,4\}$$

$$\limsup\ x_5(t) \le \frac{D}{\delta}$$

(3.6)

Thus, Ω is non-negatively invariant and the system is ultimately bounded, dissipative, with the bounds defined by the following equations.

$$\sup_{t\in[t_0,T]} x_i(t) = \max_{t\in[t_L,t_P]} \{x_{i0}, \frac{S_i + C_i - e_{i0}}{k_i}\}, \quad i = \{1,2,3,4\}$$

$$\sup_{t\in[t_0,T]} x_5(t) = \max_{t\in[t_0,T]} \{x_{50}, \frac{159D}{\delta}\} \tag{3.7}$$

This completes the proof. □

4. The Rest Points and Computation of the Jacobian Matrices

4.1 The list of rest points or physiological outcomes of HAART

In this section, the possible patho-physiological outcomes from constant continuous transdermal HAART therapy are listed and analyzed.

The physiological outcomes or the steady states during constant continuous transdermal HAART therapy occur when

$$\dot{x}_i = 0 \text{ for } i=1,2,3,4,5 \text{ and } f(t) \equiv 1$$

In particular, the clinically relevant and physiological plausible therapeutic outcomes include the following:

E_1= [0, 0, 0, 0, x_5]

E_2= [0, 0, 0, x_4, x_5]

E_3= [x_1, 0, 0, x_4, x_5]

E_4= [x_1, 0, 0, 0, x_5]

E_5= [0, x_2, x_3, 0, x_5]

E_6= [0, 0, x_3, 0, x_5]

E_7= [0, x_2, 0, 0, x_5]

E_8= [x_1, x_2, 0, 0, x_5]

E_9= [x_1, x_2, 0, x_4, x_5]

E_{10}= [x_1, x_2, x_3, x_4, x_5]

There are some other steady states which are not listed because they are less clinically interesting.

The clinically desirable steady states for a HIV-1 AIDS patient are E_3 and E_4. The steady state E_{10} depicts a person who is living with AIDS. In this case, the model exhibits persistence and the viral titer is not sufficient to annihilate the immune system. The steady states E_1 and E_2 represent scenarios of therapeutic failure because the $CD4^+$ T cells (x_1) are obliterated by the cytotoxicity of the HAART protocol. On the other hand, E_5 represents the scenario in which HIV-1 virions (x_3), HIV-1 infected $CD4^+$ T cells (x_2), and the HAART drug (x_5) eliminate the uninfected $CD4^+$ T cells (x_1), and HIV-1 specific $CD8^+$ T cells (x_4). This is also an example of therapeutic failure for HAART protocol. In E_6 and E_7, the uninfected $CD4^+$ T cells are obliterated by the HAART protocol and consequently are not clinically desirable. The steady states E_8 and E_9 represent curious scenarios because the HIV-1 virions (x_3) are eliminated from blood plasma but unfortunately the HIV-1 infected $CD4^+$ cells (x_2) remain and will constitute a reservoir from which the HIV-1 virions will burst and repopulate the blood plasma and re-infect other lymphoid organs.

The clinically desirable steady states E_3 and E_4 as well as undesirable states E_5 will be discussed in this section. The mathematical techniques used include the Hartman-Grobman theorem, non-linear dynamic systems theory, and the principles of linearized stability.

4.2 Computation of the Jacobian Matrices

Using the Hartman-Grobman theorem, it is possible to investigate the physiological stability of HIV-1 AIDS disease dynamics associated with the model equations, in the neighborhood of the physiological outcomes (steady states).

The Jacobian matrix of linearization near any physiological outcome is denoted symbolically by

$$J[E_k] := \{a_{ij}\}_{5\times 5} \in M_{5\times 5}(\Re) \quad k = 3,4,5 \tag{4.1}$$

In particular, the a_{ij} entries are defined as follows:

$$\begin{aligned}
a_{11} &:= a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - \alpha_1 x_3 - q_1 x_2 - k_1 \\
a_{12} &:= -q_1 x_1 \\
a_{13} &:= -\alpha_1 x_1 \\
a_{14} &:= 0 \\
a_{15} &:= 0 \\
a_{21} &:= a_2 x_2 (1 - b_2 x_1) e^{-b_2 x_1} - q_2 x_2 \\
a_{22} &:= a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4 - \frac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} \\
a_{23} &:= \alpha_2 x_1 - \beta_1 \\
a_{24} &:= -K_1 x_2 \\
a_{25} &:= -\frac{\xi_2 \lambda_2 \sigma_2 x_2}{(\lambda_2 + x_5)^2} \\
a_{31} &:= -\alpha_3 x_3 \\
a_{32} &:= \beta_2 x_3 \\
a_{33} &:= \beta_2 x_2 + \beta_3 - \alpha_3 x_1 - \eta_1 x_4 - k_3 - \frac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} \\
a_{34} &:= -\eta_1 x_3 \\
a_{35} &:= -\frac{\xi_3 \sigma_3 \lambda_3}{(\lambda_3 + x_5)^2} \\
a_{41} &:= a_4 x_4 (1 - b_4 x_1) e^{-b_4 x_1} \\
a_{42} &:= -K_2 x_4 \\
a_{43} &:= -\eta_2 x_4 \\
a_{44} &:= a_4 x_1 e^{-b_4 x_1} - K_2 x_2 - \eta_2 x_3 - k_4 \\
a_{45} &:= 0 \\
a_{51} &:= 0 \\
a_{52} &:= -\frac{\sigma_2 x_5}{\lambda_2 + x_5} \\
a_{53} &:= -\frac{\sigma_3 x_5}{\lambda_3 + x_5} \\
a_{54} &:= 0 \\
a_{55} &:= -\frac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} - \frac{\sigma_2 \lambda_2 x_2}{(\lambda_2 + x_5)^2} - \frac{\sigma_3 \lambda_3 x_3}{(\lambda_3 + x_5)^2}
\end{aligned} \tag{4.2}$$

The Jacobian matrices for the steady states E_3, E_4, E_5 are respectively listed as follows:

$$J\{E_1[0,0,0,0,x_5]\} =$$

$$\begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 \\ 0 & -k_2 - \dfrac{\xi_2\sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - k_3 - \dfrac{\xi_3\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & -k_4 & 0 \\ 0 & -\dfrac{\sigma_2 x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} \end{bmatrix} \tag{4.3}$$

$$J\{E_2[0,0,0,x_4,x_5]\} =$$

$$\begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 \\ 0 & -k_2 - K_1 x_4 - \dfrac{\xi_2\sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \eta_1 x_4 - k_3 - \dfrac{\xi_3\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ a_4 x_4 & -K_2 x_4 & -\eta_2 x_4 & -k_4 & 0 \\ 0 & -\dfrac{\sigma_2 x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} \end{bmatrix} \tag{4.4}$$

$$J\{E_3[x_1,0,0,x_4,x_5]\} =$$

$$\begin{bmatrix} a_1 x_1(2 - b_1 x_1)e^{-b_1 x_1} - k_1 & -q_1 x_1 & -\alpha_1 x_1 & 0 & 0 \\ 0 & a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - K_1 x_4 - \dfrac{\xi_2\sigma_2 x_5}{\lambda_2 + x_5} & \alpha_2 x_1 - \beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \alpha_3 x_1 - \eta_1 x_4 - k_3 - \dfrac{\xi_3\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ a_4 x_4(1 - b_4 x_1)e^{-b_4 x_1} & -K_2 x_4 & -\eta_2 x_4 & a_4 x_1 e^{-b_4 x_1} - k_4 & 0 \\ 0 & -\dfrac{\sigma_2 x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} \end{bmatrix} \tag{4.5}$$

$$J\{E_4[x_1,0,0,0,x_5]\} =$$

$$\begin{bmatrix} a_1 x_1(2 - b_1 x_1)e^{-b_1 x_1} - k_1 & -q_1 x_1 & -\alpha_1 x_1 & 0 & 0 \\ 0 & a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - \dfrac{\xi_2\sigma_2 x_5}{\lambda_2 + x_5} & \alpha_2 x_1 - \beta_1 & 0 & 0 \\ 0 & 0 & \beta_3 - \alpha_3 x_1 - k_3 - \dfrac{\xi_3\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & a_4 x_1 e^{-b_4 x_1} - k_4 & 0 \\ 0 & -\dfrac{\sigma_2 x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} \end{bmatrix} \tag{4.6}$$

$$J\{E_5[0,x_2,x_3,0,x_5]\} =$$

$$\begin{bmatrix} -q_1 x_2 - k_1 - \alpha_1 x_3 & 0 & 0 & 0 & 0 \\ a_2 x_2 - q_2 x_2 & -k_2 - \dfrac{\xi_2\sigma_2 x_5}{\lambda_2 + x_5} & -\beta_1 & -K_1 x_2 & -\dfrac{\xi_2\lambda_2\sigma_2 x_2}{(\lambda_2 + x_5)^2} \\ -\alpha_3 x_3 & \beta_2 x_3 & \beta_2 x_2 + \beta_3 - k_3 - \dfrac{\xi_3\sigma_3 x_5}{\lambda_3 + x_5} & -\eta_1 x_3 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & -K_2 x_2 - \eta_2 x_3 - k_4 & 0 \\ 0 & -\dfrac{\sigma_2 x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3 x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} - \dfrac{\sigma_2\lambda_2 x_2}{(\lambda_2 + x_5)^2} - \dfrac{\sigma_3\lambda_3 x_3}{(\lambda_3 + x_5)^2} \end{bmatrix}$$

(4.7)

$$J\{E_7[0, x_2, 0, 0, x_5]\} =$$

$$\begin{bmatrix} -q_1x_2 - k_1 & 0 & 0 & 0 & 0 \\ a_2x_2 - q_2x_2 & -k_2 - \dfrac{\xi_2\sigma_2x_5}{\lambda_2 + x_5} & -\beta_1 & -K_1x_2 & -\dfrac{\xi_2\lambda_2\sigma_2x_2}{(\lambda_2 + x_5)^2} \\ 0 & 0 & \beta_2x_2 + \beta_3 - k_3 - \dfrac{\xi_3\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ 0 & 0 & 0 & -K_2x_2 - k_4 & 0 \\ 0 & -\dfrac{\sigma_2x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} - \dfrac{\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} \end{bmatrix} \tag{4.8}$$

$$J\{E_9[x_1, x_2, 0, x_4, x_5]\} =$$

$$\begin{bmatrix} a_1x_1(2 - b_1x_1)e^{-b_1x_1} + q_1x_2 - k_1 & -q_1x_1 & -\alpha_1x_1 & 0 & 0 \\ a_2x_2(1 - b_2x_1)e^{-b_2x_1} + q_2x_2 & a_2x_1e^{-b_2x_1} - q_2x_1 - k_2 - K_1x_4 - \dfrac{\xi_2\sigma_2x_5}{\lambda_2 + x_5} & \alpha_2x_1 - \beta_1 & -K_1x_2 & -\dfrac{\xi_2\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} \\ 0 & 0 & \beta_2x_2 + \beta_3 - \alpha_3x_1 - \eta_1x_4 - k_3 - \dfrac{\xi_3\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\xi_3\sigma_3\lambda_3}{(\lambda_3 + x_5)^2} \\ a_4x_4(1 - b_4x_1)e^{-b_4x_1} & -K_2x_4 & -\eta_2x_4 & a_4x_1e^{-b_4x_1} + K_2x_2 - k_4 & 0 \\ 0 & -\dfrac{\sigma_2x_5}{\lambda_2 + x_5} & -\dfrac{\sigma_3x_5}{\lambda_3 + x_5} & 0 & -\dfrac{\sigma_0\lambda_0}{(\lambda_0 + x_5)^2} - \dfrac{\sigma_2\lambda_2x_2}{(\lambda_2 + x_5)^2} \end{bmatrix} \tag{4.9}$$

5. Necessary Criteria for Various Therapeutic Outcomes of AIDS during HAART

In this section, the necessary mathematical criteria for all therapeutic outcomes during HAART are computed and presented in the form of theorems.

Theorem 5.1. Suppose

(i)
$$\begin{cases} S_1 + a_1\hat{x}_1^2e^{-b_1\hat{x}_1} - k_1\hat{x}_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 + a_4\hat{x}_1\hat{x}_4e^{-b_4\hat{x}_1} - k_4\hat{x}_4 - e_{40} = 0 \\ D - \dfrac{\sigma_0\hat{x}_5}{\lambda_0 + \hat{x}_5} - k_5\hat{x}_5 = 0 \end{cases} \tag{5.1}$$

(ii)
$$\begin{cases} a_1x_1(2 - b_1x_1)e^{-b_1x_1} - k_1 < 0 \\ a_2x_1e^{-b_2x_1} - q_2x_1 - k_2 - \dfrac{\xi_2\sigma_2x_5}{\lambda_2 + x_5} < 0 \\ \beta_3 - \alpha_3x_1 - k_3 - \dfrac{\xi_3\sigma_3x_5}{\lambda_3 + x_5} < 0 \\ a_4x_1e^{-b_4x_1} - k_4 < 0 \end{cases} \tag{5.2}$$

The HAART therapeutic outcome $E_4[x_1, 0, 0, 0, x_5]$ exists and it is a local attractor.

Proof. Consider the model equations (3.1). Then criterion (5.1) is a necessary condition for the existence of $E_4[x_1, 0, 0, 0, x_5]$. Now the Jacobian matrix of linearization of the model equations in the neighborhood of $E_4[x_1, 0, 0, 0, x_5]$ is such that the eigenvalues are given by the following expressions.

$$\begin{cases} \lambda_1 = a_1 x_1 (2 - b_1 x_1) e^{-b_1 x_1} - k_1 \\ \lambda_2 = a_2 x_1 e^{-b_2 x_1} - q_2 x_1 - k_2 - \dfrac{\xi_2 \sigma_2 x_5}{\lambda_2 + x_5} \\ \lambda_3 = \beta_3 - \alpha_3 x_1 - k_3 - \dfrac{\xi_3 \sigma_3 x_5}{\lambda_3 + x_5} \\ \lambda_4 = a_4 x_1 e^{-b_4 x_1} - k_4 \\ \lambda_5 = -\dfrac{\sigma_0 \lambda_0}{(\lambda_0 + x_5)^2} \end{cases} \tag{5.3}$$

The eigenvalues have negative real parts when criterion (4.2) holds. Thus, two criteria (5.1) and (5.2) constitute the necessary conditions for the local existence of $E_4[x_1, 0, 0, 0, x_5]$. In particular, the principles of linearized stability of dynamical systems can be used to imply that the rest point $E_4[x_1, 0, 0, 0, x_5]$ is locally asymptotically stable and hence a local attractor. □

Clinical Implication 5.1. The criteria (5.1) and (5.2) guarantee a temporary cure for the AIDS patient. There will be a finite time interval during which the HIV-1 virions will be annihilated from the patient's blood plasma. This will however be short-lived because the rest point $E_4[x_1, 0, 0, 0, x_5]$ may become unstable and the criteria for temporal cure are violated. It is possible for therapeutic criteria to be derived to maintain the patient to be permanently free of AIDS, which we shall discuss in Theorem 5.5.

Theorem 5.2. Suppose

(i)
$$\begin{cases} S_1 - e_{10} = 0 \\ S_2 - k_2 \bar{x}_2 - \beta_1 \bar{x}_3 - e_{20} - \dfrac{\xi_2 \sigma_2 \bar{x}_2 \bar{x}_5}{\lambda_2 + x_5} = 0 \\ S_3 + \beta_2 \bar{x}_2 \bar{x}_3 + \beta_3 \bar{x}_3 - k_3 \bar{x}_3 - e_{30} - \dfrac{\xi_3 \sigma_3 \bar{x}_3 \bar{x}_5}{\lambda_3 + \bar{x}_5} = 0 \\ S_4 - e_{40} = 0 \\ D - \dfrac{\sigma_0 \bar{x}_5}{\lambda_0 + \bar{x}_5} - \dfrac{\sigma_2 \bar{x}_2 \bar{x}_5}{\lambda_2 + \bar{x}_5} - \dfrac{\sigma_3 \bar{x}_3 \bar{x}_5}{\lambda_3 + \bar{x}_5} - k_5 \bar{x}_5 = 0 \end{cases} \tag{5.4}$$

(ii) Let $\sigma(J\{E_5[0, x_2, x_3, 0, x_5]\})$ be the eigen-spectrum of

$$J\{E_5[0, x_2, x_3, 0, x_5]\} := \begin{vmatrix} \bar{a}_{11} & \bar{a}_{12} & \bar{a}_{13} & \bar{a}_{14} & \bar{a}_{15} \\ \bar{a}_{21} & \bar{a}_{22} & \bar{a}_{23} & \bar{a}_{24} & \bar{a}_{25} \\ \bar{a}_{31} & \bar{a}_{32} & \bar{a}_{33} & \bar{a}_{34} & \bar{a}_{35} \\ \bar{a}_{41} & \bar{a}_{42} & \bar{a}_{43} & \bar{a}_{44} & \bar{a}_{45} \\ \bar{a}_{51} & \bar{a}_{52} & \bar{a}_{53} & \bar{a}_{54} & \bar{a}_{55} \end{vmatrix} \tag{5.5}$$

such that

$$\sigma(J\{E_5[0, x_2, x_3, 0, x_5]\}) = \{\lambda_i \mid \lambda^3 + \bar{a}_1 \lambda^2 + \bar{a}_2 \lambda + \bar{a}_3 = 0, i = 1, 2, 3\} \cup \{\lambda_4, \lambda_5\} \tag{5.6}$$

where

$$\begin{cases} \overline{a}_1 = -Trace\{J\{E_5[0, x_2, x_3, 0, x_5]\}\} \\ \overline{a}_2 = \det\begin{vmatrix} \overline{a}_{33} & \overline{a}_{35} \\ \overline{a}_{53} & \overline{a}_{55} \end{vmatrix} + \det\begin{vmatrix} \overline{a}_{22} & \overline{a}_{25} \\ \overline{a}_{31} & \overline{a}_{33} \end{vmatrix} + \det\begin{vmatrix} \overline{a}_{22} & \overline{a}_{23} \\ \overline{a}_{32} & \overline{a}_{33} \end{vmatrix} \\ \overline{a}_3 = -\det J\{E_5[0, x_2, x_3, 0, x_5]\} \\ \lambda_4 = \overline{a}_{11} \\ \lambda_5 = \overline{a}_{44} \end{cases} \tag{5.7}$$

Then the rest point E_5= [0, x_2, x_3, 0, x_5] is locally asymptotically stable if

$$\overline{a}_1 > 0, \ \overline{a}_3 > 0, \ \overline{a}_1\overline{a}_2 > \overline{a}_3 \tag{5.8}$$

Proof. The physiological outcome or rest point E_5 exists if criterion (5.4) is satisfied. The Hartmann-Grobman theorem as applied in [10] in addition to the principles of linearized stability can be applied to the model equations in the neighborhood of E_5. The eigen-spectrum of the Jacobian matrix of the linearization is given by (5.6). Then the Routh-Hurwitz criterion [10] can be applied to (5.6) with definitions stated by (5.7). Thus, Theorem (5.2) follows immediately.

Clinical Implication 5.2. This theorem depicts the conditions for one of the worst scenarios during AIDS therapy using continuous infusion HAART. If the conditions (5.4) and (5.8) hold, then the HAART therapy annihilated all the uninfected CD_4^+ T cells, and HIV-1 specific cytotoxic CD_8^+ T cells. Consequently, the immune system of the AIDS patient becomes incapacitated and the patient becomes the target of opportunistic infections. However, this situation may not last very long but could be fatal.

Theorem 5.3. Suppose

(i)
$$\begin{cases} S_1 - e_{10} = 0 \\ S_2 - e_{20} = 0 \\ S_3 - e_{30} = 0 \\ S_4 - e_{40} = 0 \\ D - \dfrac{\sigma_0 \tilde{x}_5}{\lambda_0 + \tilde{x}_5} - k_5 \tilde{x}_5 = 0 \end{cases} \tag{5.9}$$

The HAART therapeutic outcome E_1[0, 0, 0, 0, x_5] exists and it is a local attractor.

Proof. The proof follows directly from the definition of the rest point and inspection of the eigen-spectrum of the Jacobian matrix of linearization of the model equations in the neighborhood of E_1.

Clinical Implication 5.3. If the HAART protocol used for the AIDS patient is such that condition (5.9) is satisfied, then the patient experiences extreme immune system cytotoxicity in which the uninfected CD_4^+ T cells, HIV-1 specific cytotoxic CD_8^+ T cells, HIV-1 virions, and HIV-1 infected CD4+ T cells are all decimated. This is not a therapeutically desirable clinical outcome, because the patient may become severely incapacitated. To avoid this scenario, the HAART therapy must implemented in such a way that criterion (5.9) is violated.

Let $\sigma(J\{E_3[x_1,0,0,x_4,x_5]\}$ be the eigen-spectrum for the Jacobian matrix $(J\{E_3[x_1,0,0,x_4,x_5]\}$ such that

$$\sigma(J\{E_3[x_1,0,0,x_4,x_5]\}) = \{\lambda_k \mid \det \mid J(E_3) - \lambda I \mid = 0, k = 1,2,3,4,5\}$$

Theorem 5.4. Suppose

(i)
$$\begin{cases} S_1 - e_{10} = k_1\bar{x}_1 - a_1\bar{x}_1^2 e^{-b_1\bar{x}_1} \\ S_4 - e_{40} = k_4\bar{x}_4 - a_4\bar{x}_1\bar{x}_4 e^{-b_4\bar{x}_1} \\ D = \dfrac{\sigma_0\bar{x}_5}{\lambda_0 + \bar{x}_5} \end{cases} \tag{5.10}$$

(ii) The eigenvalues of $(J\{E_3[x_1,0,0,x_4,x_5]\}$, represented by $\lambda_k = \alpha_k + i\beta_k$, are such that the $Re(\lambda_k) < 0$.

Then the rest point of E3 exists and is a local attractor.

Proof. The condition (i) guarantees the local existence of E3. The principles of linearized stability can be used to show that condition (ii) ensures that E3 is locally asymptotically stable and hence is a local attractor. □

Next, the interior rest point E10 is considered. This describes a situation in which the patient survives for a long time with AIDS. It is possible during HAART that, the HIV-1 virions cannot be annihilated but instead the system persists in a chronic configuration in which the blood plasma levels of the HIV-1 virions co-exist with the other clinically measurable parameters such as uninfected CD4+ T cells, the HIV-1 infected CD4+ T cells, HIV-1 specific CD8+ T cells, and HAART drug molecules. The criteria for existence of E10 are listed in the following theorem.

Theorem 5.5. Let

(i)
$$\begin{cases} m_i = \inf\limits_{t\in[t_0,T]}\left\{a_i\breve{x}_1\breve{x}_i e^{-b_i\breve{x}_1}\right\} \quad where \quad i = \{1,2,4\} \\ L_1 = \sup\limits_{t\in[t_0,T]}\left\{\alpha_1\breve{x}_3 + q_1\breve{x}_2 + k_1\right\} \\ L_2 = \sup\limits_{t\in[t_0,T]}\left\{q_2\breve{x}_1 + k_2 + K_1\breve{x}_4 + \dfrac{\xi_2\sigma_2\breve{x}_2\breve{x}_5}{\lambda_2 + \breve{x}_5}\right\} \\ U_1 = \sup\limits_{t\in[t_0,T]}\left\{\beta_1\breve{x}_3\right\} \\ L_3 = \sup\limits_{t\in[t_0,T]}\left\{\alpha_3\breve{x}_1 + \eta_1\breve{x}_4 + k_3 + \dfrac{\xi_3\sigma_3}{\lambda_3 + \breve{x}_5}\right\} \\ m_3 = \inf\limits_{t\in[t_0,T]}\left\{\beta_2\breve{x}_2\breve{x}_3 + \beta_3\breve{x}_3\right\} \\ L_4 = \inf\limits_{t\in[t_0,T]}\left\{K_2\breve{x}_2 + \eta_2\breve{x}_3 + k_4\right\} \\ L_5 = \inf\limits_{t\in[t_0,T]}\left\{\dfrac{\sigma_0}{\lambda_0 + \breve{x}_5} + \dfrac{\sigma_2\breve{x}_2}{\lambda_2 + \breve{x}_5} + \dfrac{\sigma_3\breve{x}_3}{\lambda_3 + \breve{x}_5}\right\} \end{cases} \tag{5.11}$$

(ii)
$$\begin{cases} \lim\ \inf\ x_1 \geq \dfrac{S_1 + m_1 - e_{10}}{L_1} > 0 \\ \lim\ \inf\ x_2 \geq \dfrac{S_2 + m_2 - U_1 - e_{20}}{L_2} > 0 \\ \lim\ \inf\ x_3 \geq \dfrac{S_3 + m_3 - e_{30}}{L_3} > 0 \\ \lim\ \inf\ x_4 \geq \dfrac{S_4 + m_4 - e_{40}}{L_4} > 0 \\ \lim\ \inf\ x_5 \geq \dfrac{D}{L_5} > 0 \end{cases} \tag{5.12}$$

Then the system $[x_1, x_2, x_3, x_4, x_5]$ will persist and the HAART therapeutic outcome $E_{10}=[\breve{x}_1, \breve{x}_2, \breve{x}_3, \breve{x}_4, \breve{x}_5]$ exists.

Proof. For a proof refer to Nani and Jin[10]. □

Clinical Implication 5.4. If uninfected CD_4^+ T cells, infected CD4+ T cells, the HIV-1 viral mRNA copies in the blood plasma, HIV-1 specific cytotoxic CD_8^+ T cells, and the HAART drug concentration are within certain thresholds, then the AIDS patient will live with AIDS. If any of the conditions listed in (5.11) are violated, the patient will experience unpredictable therapeutic outcomes including full-blown AIDS or spontaneous elimination of HIV-1 virions.

6. Sufficient Criteria for Permanent Cure of AIDS during HAART

In this section, the sufficient criteria for permanent annihilation of HIV-1 virions during HAART will be derived. The clinically desirable physiological outcomes are $E_4[x_1, 0, 0, 0, x_5]$ and $E_3= [x_1, 0, 0, x_4, x_5]$. It must be recalled that E4 corresponds to the physiological outcome in which HIV-1 infected CD4+ T cells, the HIV-1 virions in the blood plasma and HIV-1 specific CD8+ T cells are eliminated in the blood plasma of the AIDS patient. The sufficient criteria for E4 will be discussed first.

The rest point E4 will be analyzed for global asymptotical stability in the space $R_+^{x_1 x_5} = [x_1, x_5 \mid x_1 \geq 0, x_5 \geq 0]$

The model equations (3.1) correspondingly reduce to the following:

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_5 = D - \dfrac{\sigma_0 x_5}{\lambda_0 + x_5} \\ x_i(t_0) = x_{i0} \quad for \quad i = \{1,\ 5\} \end{cases} \tag{6.1}$$

Consider the Liapunov functional:

$$V := \sum \frac{1}{2} \hat{c}_i (x_i - \hat{x}_i)^2 \qquad where \quad i = \{1, 5\} \ and \ \hat{c}_i \in R_+ = (0, \infty) \tag{6.2}$$

The derivative of V along the solution curves of the model equations yields the result:

$$\begin{aligned} \overset{*}{V} &= \hat{c}_1 (x_1 - \hat{x}_1) \dot{x}_1 + \hat{c}_5 (x_5 - \hat{x}_5) \dot{x}_5 \\ &= \hat{c}_1 (x_1 - \hat{x}_1)(S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10}) + \\ &\hat{c}_5 (x_5 - \hat{x}_5)(D - \frac{\sigma_0 x_5}{\lambda_0 + x_5}) \end{aligned} \tag{6.3}$$

But at a steady state, the following equations hold.

$$\begin{cases} S_1 - e_{10} = k_1 \hat{x}_1 - a_1 \hat{x}_1^2 e^{-b_1 \hat{x}_1} \\ D = \dfrac{\sigma_0 \hat{x}_5}{\lambda_0 + \hat{x}_5} \end{cases} \tag{6.4}$$

Define the following Lebesgue measurable, functions which are of bounded variation:

$$\begin{aligned} G(x_1) &= a_1 x_1^2 e^{-b_1 x_1} \\ L(x_5) &= \frac{\sigma_0 x_5}{\lambda_0 + x_5} \end{aligned} \tag{6.5}$$

$$\dot{V} = \hat{c}_1(x_1 - \hat{x}_1)\dot{x}_1 + \hat{c}_5(x_5 - \hat{x}_5)\dot{x}_5$$

$$= \hat{c}_1(x_1 - \hat{x}_1)(-a_1\hat{x}_1^2 e^{-b_1 x_1} + k_1\hat{x}_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1) + \hat{c}_5(x_5 - \hat{x}_5)\left(\frac{\sigma_0 \hat{x}_5}{\lambda_0 + \hat{x}_5} - \frac{\sigma_0 x_5}{\lambda_0 + x_5}\right) \quad (6.6)$$

$$= \hat{c}_1(x_1 - \hat{x}_1)[G(x_1) - G(\hat{x}_1)] + \hat{c}_1(x_1 - \hat{x}_1)(k_1\hat{x}_1 - k_1 x_1)]$$
$$+ \hat{c}_5(x_5 - \hat{x}_5)[L(\hat{x}_5) - L(x_5)]$$

$$\dot{V} = -\hat{c}_1 k_1 (x_1 - \hat{x}_1)^2 + \hat{c}_1(x_1 - \hat{x}_1)[G(x_1) - G(\hat{x}_1)] - \sigma_0 \hat{c}_5(x_5 - \hat{x}_5)[L(x_5) - L(\hat{x}_5)] \quad (6.7)$$

Let

$$v_1 = x_1 - \hat{x}_1$$
$$v_2 = x_5 - \hat{x}_5 \quad (6.8)$$

and

$$X = \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} \in R_+^2 \quad (6.9)$$

and define define $A=\{a_{ij}\} \in M_{2X2}(R)$ such that

$$A = \begin{bmatrix} a_{11} & \frac{1}{2}a_{12} \\ \frac{1}{2}a_{21} & a_{22} \end{bmatrix}$$

then

$$\dot{V} := a_{11}v_1^2 + \frac{1}{2}a_{12}v_1 v_2 + \frac{1}{2}a_{21}v_2 v_1 + a_{22}v_2^2 \quad (6.10)$$
$$= X^T A X$$

Where X^T denotes the transpose of X and $\dot{V}$ is negative definite if the eigenvalues of A have negative real parts or satisfy the conditions of $a_{11} < 0$ and det $(A) > 0$ [???].

In particular, the $[a_{ij}]_{2x2}$ are defined as follows:

$$\begin{cases} a_{11} := -[\hat{c}_1 k_1 - \hat{c}_1\left(\frac{G(x_1) - G(\hat{x}_1)}{x_1 - \hat{x}_1}\right)] \\ a_{12} = a_{21} = 0 \\ a_{22} := -\hat{c}_5\left[\frac{L(x_5) - L(\hat{x}_5)}{x_5 - \hat{x}_5}\right] \end{cases} \quad (6.11)$$

As the flow dynamics approaches the steady state $E_4[x_1, 0, 0, 0, x_5]$, the following conditions hold:

$$a_{11} \to -[\hat{c}_1 k_1 - G_1'(\hat{x}_1)]$$
$$a_{22} \to -\hat{c}_5 L'(\hat{x}_5) \quad (6.12)$$

where

$$G'(\hat{x}_1) = a_1\hat{x}_1 e^{-b_1\hat{x}_1}(2 - b_1\hat{x}_1)$$

$$L'(\hat{x}_5) = \frac{\sigma_0\lambda_0}{(\lambda_0 + \hat{x}_5)^2} > 0$$

In particular,

$$G'(\hat{x}_1) = \begin{cases} > 0 \ if \ \ \hat{x}_1 < 2/b_1 \\ = 0 \ if \ \ \hat{x}_1 = 2/b_1 \\ < 0 \ if \ \ \hat{x}_1 > 2/b_1 \end{cases}$$

The sufficient criteria for the global asymptotic stability of E_4 are specified in the following theorem.

Theorem 6.1 Let

(i) Conditions (5.1) and (5.2) hold,

(ii) Suppose $\hat{x}_1 < 2/b_1$ holds,

then the rest point E_4 is a global attractor such that the HIV-1 virions, HIV-1 infected CD4+ T cells, HIV-1 specific CD8+ T cells are annihilated during HAART.

Proof. Condition (i) guarantees the local existence and local asymptotic stability of E_4. If condition (ii) holds, then eigenvalues of the matrix A has negative real parts, and consequently, $\overset{*}{V}$ is negative definite. Hence, the theorem holds. □

Clinical Implication 6.1

(i) The criterion $\hat{x}_1 < 2/b_1$ is a sufficient condition for annihilation of HIV-1 virions of the blood plasma of AIDS patient during HAART.

(ii) The function $G(\hat{x}_1)$ is a measure of the rate at which the CD4+ T cells (x_1) are activated by interleukin-2 (IL-2) in an autocrine process when the physiological flow during HAART tends to E_4. It is possible to attach a biochemical measure to coefficient a_1 and b_1 of $G(\hat{x}_1)$. This can be done as follows:

$$G(\hat{x}_1) = a_1\hat{x}_1{}^2 e^{-b_1\hat{x}_1} = \frac{a_1\hat{x}_1{}^2}{e^{b_1\hat{x}_1}} = \frac{a_1\hat{x}_1\hat{x}_1}{1 + b_1\hat{x}_1 + \frac{(b_1\hat{x}_1)^2}{2!} + \ldots} \approx \frac{a_1\hat{x}_1\hat{x}_1}{1 + b_1\hat{x}_1} = \frac{\frac{a_1}{b_1}\hat{x}_1\hat{x}_1}{\frac{1}{b_1} + \hat{x}_1}$$

$$= \frac{V_{\max}\hat{x}_1\hat{x}_1}{K_m + \hat{x}_1}$$

Where $K_m = \frac{1}{b_1}$ is approximately equal to the Michaelis-Menten constant of the CD4+ T cells activation reaction by interleukin-2, and V_{max} represents the maximal velocity of the CD4+ T cells IL-2 activation reaction.

(iii) Note that k_1 is the rate of degradation and decay of the CD4+ T cells during AIDS. Thus the theorem implies that if the rate of degradation of CD4+ T cells is greater than the rate of IL-2 activation of T cells and if in addition, the number of the CD4+ T cells are such that $\hat{x}_1 < 2K_m$, then the patient will be cured of AIDS.

Next, the other clinical desirable rest point E_3= [x_1, 0, 0, x_4, x_5] is analyzed. The aim is to find the sufficient criteria under which the HIV-1 virions in the blood plasma, the HIV-1 infected CD4+ T cells are annihilated but the HIV-1 specific CD8+ T cells will persist as memory T cells as well as the CD4+ T cells and some drug residues will remain in the AIDS patient. It is expected that the CD4+ T cells will eventually repopulate to their carrying capacity whereas the drug residues will ultimately dissipate. The analysis will be similar to the preceding one for E_4.

The restriction of the model equations to the space $R_+^{x_1 x_4 x_5} = [x_1, x_4, x_5 \mid x_1 \geq 0, x_4 \geq 0, x_5 \geq 0]$ leads to the following equations [nani and jin].

$$\begin{cases} \dot{x}_1 = S_1 + a_1 x_1^2 e^{-b_1 x_1} - k_1 x_1 - e_{10} \\ \dot{x}_4 = S_4 + a_4 x_1 x_4 e^{-b_4 x_1} - k_4 x_4 - e_{40} \\ \dot{x}_5 = D - \dfrac{\sigma_0 x_5}{\lambda_0 + x_5} \\ x_i(t_0) = x_{i0} \quad for \quad i = \{1, 4, 5\} \end{cases} \tag{6.13}$$

Consider the Liapnnov functional:

$$V := \sum \frac{1}{2} \bar{c}_i (x_i - \bar{x}_i)^2 \tag{6.14}$$
$$where \quad i = \{1,4,5\} \; and \; c_i \in R_+ = (0, \infty)$$

The derivative of V along the solution curves of the model equations yields the result:

$$\overset{*}{V} = \bar{c}_1 (x_1 - \bar{x}_1) \dot{x}_1 + \bar{c}_4 (x_4 - \bar{x}_4) \dot{x}_4 + \bar{c}_5 (x_5 - \bar{x}_5) \dot{x}_5$$

Thus a steady state, $\dot{x}_i = 0$ and the following equations hold.

$$\begin{cases} S_1 - e_{10} = k_1 \bar{x}_1 - a_1 \bar{x}_1^2 e^{-b_1 \bar{x}_1} \\ S_4 - e_{40} = k_4 \bar{x}_4 - a_4 \bar{x}_1 \bar{x}_4 e^{-b_4 \bar{x}_1} \\ D = \dfrac{\sigma_0 \bar{x}_5}{\lambda_0 + \bar{x}_5} \end{cases} \tag{6.15}$$

Thus

$$\begin{aligned} \overset{*}{V} &= \bar{c}_1 k_1 (x_1 - \bar{x}_1)(\bar{x}_1 - x_1) \\ &\quad + \bar{c}_1 (x_1 - \bar{x}_1)[G(\bar{x}_1) - G(x_1)] \\ &\quad + \bar{c}_4 k_4 (x_4 - \bar{x}_4)(\bar{x}_4 - x_4) \\ &\quad + \bar{c}_4 (x_4 - \bar{x}_4)[F(\bar{x}_1, \bar{x}_4) - F(x_1, x_4)] \\ &\quad + \bar{c}_5 \sigma_0 [L(\bar{x}_5) - L(x_5)] \\ &where \\ &\quad G(x_1) = a_1 x_1^2 e^{-b_1 x_1} \\ &\quad F(x_1, x_4) = a_4 x_1 x_4 e^{-b_4 x_1} \\ &\quad L(x_5) = \frac{\sigma_0 x_5}{\lambda_0 + x_5} \end{aligned} \tag{6.16}$$

The functions *G, F, L* are continuous, Lebesgue measurable, and of bounded variations.

Let $\overset{*}{V} = X^T C X$ (6.17)

where

and

$$\begin{aligned} X &= \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} \in R_+^3 \\ u_1 &= x_1 - \bar{x}_1 \\ u_2 &= x_4 - \bar{x}_4 \\ u_3 &= x_5 - \bar{x}_5 \end{aligned} \tag{6.18}$$

such that X^T denotes the transpose of X. Define $C \in M_{3x3}(R)$ such that

$$C = \begin{bmatrix} c_{11} & \frac{1}{2}c_{12} & \frac{1}{2}c_{13} \\ \frac{1}{2}c_{12} & c_{22} & \frac{1}{2}c_{23} \\ \frac{1}{2}c_{13} & \frac{1}{2}c_{23} & c_{33} \end{bmatrix} \tag{6.19}$$

Now

$$\begin{aligned} \overset{*}{V} := & c_{11}u_1^2 + \frac{1}{2}c_{12}u_1u_2 + \frac{1}{2}c_{13}u_1u_3 \\ & + \frac{1}{2}c_{12}u_2u_1 + c_{22}u_2^2 + \frac{1}{2}c_{23}u_2u_3 \\ & + \frac{1}{2}c_{13}u_3u_1 + \frac{1}{2}c_{23}u_3u_2 + c_{33}u_3^2 \end{aligned} \tag{6.20}$$

Where the $[c_{ij}]_{3x3}$ are defined as follows:

$$\begin{cases} c_{11} := -[\bar{c}_1 k_1 - c_1(\dfrac{G(x_1) - G(\bar{x}_1)}{x_1 - \bar{x}_1})] \\ c_{12} := -c_4[\dfrac{F(x_1, x_4) - F(\bar{x}_1, \bar{x}_4)}{x_1 - \bar{x}_1}] = c_{21} \\ c_{13} = c_{31} = 0 \\ c_{22} = -\bar{c}_4 k_4 \\ c_{23} = c_{32} = 0 \\ c_{33} := -c_5[\dfrac{L(x_5) - L(\bar{x}_5)}{x_5 - \bar{x}_5}] \end{cases} \tag{6.21}$$

As the flow associated with the model equations approaches $E_3 = [\bar{x}_1, 0, 0, \bar{x}_4, \bar{x}_5]$, the matrix entries $[c_{ij}]_{3x3}$ have the following form:

$$\begin{aligned} & c_{11} \to -[\bar{c}_1 k_1 - \bar{c}_1 G'(\bar{x}_1)] \\ & c_{12} \to -c_4[F_{x_1}(\bar{x}_1, \bar{x}_4)] \\ & c_{22} = -\bar{c}_4 k_4 \\ & c_{33} \to -\bar{c}_5 L'(\bar{x}_5) \end{aligned} \tag{6.22}$$

But it can be shown that

$$\begin{aligned} & F_{x_1}(\bar{x}_1, \bar{x}_4) = a_4 \bar{x}_4 e^{-b_4 \bar{x}_1}(1 - \bar{x}_1 b_4) \\ & G'(\bar{x}_1) = a_1 \bar{x}_1 e^{-b_1 \bar{x}_1}(2 - \bar{x}_1 b_1) \\ & L'(\bar{x}_5) = \frac{\sigma_0 \lambda_0}{(\lambda_0 + \bar{x}_5)^2} > 0 \end{aligned} \tag{6.23}$$

In particular, (cf. [nani and jin])

$$F_{x_1}(\bar{x}_1, \bar{x}_4) = \begin{cases} > 0 \; if \; \bar{x}_1 < \frac{1}{b_4} \\ = 0 \; if \; \bar{x}_1 = \frac{1}{b_4} \\ < 0 \; if \; \bar{x}_1 > \frac{1}{b_4} \end{cases} \tag{6.24}$$

Similarly,

$$G'(\bar{x}_1) = \begin{cases} > 0 \; if \;\; \bar{x}_1 < \frac{2}{b_1} \\ = 0 \; if \;\; \bar{x}_1 = \frac{2}{b_1} \\ < 0 \; if \;\; \bar{x}_1 > \frac{2}{b_1} \end{cases} \tag{6.25}$$

Using the specifications in (4.31), the matrix C has the form

$$C = \begin{bmatrix} c_{11} & \frac{1}{2}c_{12} & 0 \\ \frac{1}{2}c_{12} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{bmatrix} \tag{6.26}$$

The matrix C is negative definite if the following criteria hold:

$$\begin{aligned} &i. \quad C_1 = \det c_{11} < 0 \quad or \quad c_{11} < 0 \\ &ii. \quad C_2 = \det \begin{vmatrix} c_{11} & \frac{1}{2}c_{12} \\ \frac{1}{2}c_{12} & c_{22} \end{vmatrix} > 0 \quad or \quad c_{11}c_{22} - \tfrac{1}{4}(c_{12})^2 > 0 \\ &iii. \quad C_3 = \det \begin{vmatrix} c_{11} & \frac{1}{2}c_{12} & 0 \\ \frac{1}{2}c_{12} & c_{22} & 0 \\ 0 & 0 & c_{33} \end{vmatrix} < 0 \quad or \quad c_{33}[c_{11}c_{22} - \tfrac{1}{4}(c_{12})^2] < 0 \end{aligned} \tag{6.27}$$

Theorem 6.2. Suppose $\bar{x}_1 = \dfrac{1}{b_4} < \dfrac{2}{b_1}$

Then the physiological steady state E_3=[$\bar{x}_1$, 0, 0, $\bar{x}_4$, $\bar{x}_5$] is globally asymptotically stable and a global attractor.

Proof. The condition (6.27) *i.* holds when $k_1 > G'(\bar{x}_1) > 0$. But $G'(\bar{x}_1) > 0$ when $\bar{x}_1 < \frac{2}{b_1}$. Observe that if $\bar{x}_1 = \frac{1}{b_4}$, then $c_{12} = 0$ and condition (6.27) *ii.* holds. Since $c_{33} < 0$ and $c_{12} = 0$, the condition (4.37) also holds immediately. Hence the theorem follows. □

Clinical Implications 6.2.

(i) Theorem 4.6 gives the sufficient theoretical criteria for the HIV-1 infected CD4+ T cells and HIV-1 virions in the blood plasma to be eradicated during HAART. This theorem also provides the conditions under which HIV-1 specific CD8+ T cells will persist as memory cells after the HAART therapy.

(ii) It is possible to express the conditions of Theorem 4.6 in terms of clinically measurable biophysical parameters. By using Taylor expansions of $e^{-b_1\bar{x}_1}$ and $e^{-b_4\bar{x}_1}$, the conditions $\bar{x}_1 = \dfrac{1}{b_4} < \dfrac{2}{b_1}$ is approximately equivalent to the expression

$$\bar{x}_1 = K_m^{CD8+} < 2K_m^{CD4+} \tag{6.28}$$

This can be interpreted to mean that HAART will cure the AIDS patient if the number density of uninfected CD4+ T cells is equal to the Michaelis-Menten constant of the IL-2 activation of the CD8+ T cells, which in turn has to be less than twice Michaelis-Menten constant of the IL-2 activation of the CD4+ T cells.

Corollary 6.2. Suppose $\bar{x}_1 = \dfrac{1}{b_4} = \dfrac{2}{b_1}$

Then the physiological steady state E_3=[$\bar{x}_1$, 0, 0, $\bar{x}_4$, $\bar{x}_5$] is a global attractor.

Proof. The conditions (4.37) *i, ii, iii* hold if the theorem hypothesis is satisfied. This makes the matrix C in (4.27) negative definite. Consequently, the steady state becomes global attractor. □

It is possible to combine Theorem 4.6 and Corollary 4.6 to obtain the combines criteria:

571 $$\bar{x}_1 = \frac{1}{b_4} \leq \frac{2}{b_1}$$

572 $$\bar{x}_1 \approx K_m^{CD8+} < 2K_m^{CD4+}$$

573

574 7. Simulation Results

575 In this section investigative computer simulations will be presented and discussed . These simulations are
576 performed using clinically plausible hypothetical patient patho-physiological parametric configurations. The numerical
577 estimates used are variations of estimates published in the references: [2,11,13,15]. Some techniques for estimating HIV-I
578 dynamical parameters have been described by Ciupe et al. [2]. It must be emphasized that every AIDS patient has a unique
579 situation and therefore these simulation results are hypothetical scenarios and depict non-equilibrium disease configurations
580 but do not depict the equilibrium AIDS configurations represented by the necessary and sufficient theorems discussed in
581 section 6. However the investigative computer simulations elucidate several dynamical aspects of HIV-1 AIDS dynamics
582 which are based on the respective parametric configurations . In a future publication the equilibrium parametric configuration
583 simulations will be presented. The x-axis of the simulation graphs is calibrated in months.

584 7.1 Simulation results for hypothetical AIDS patient #1

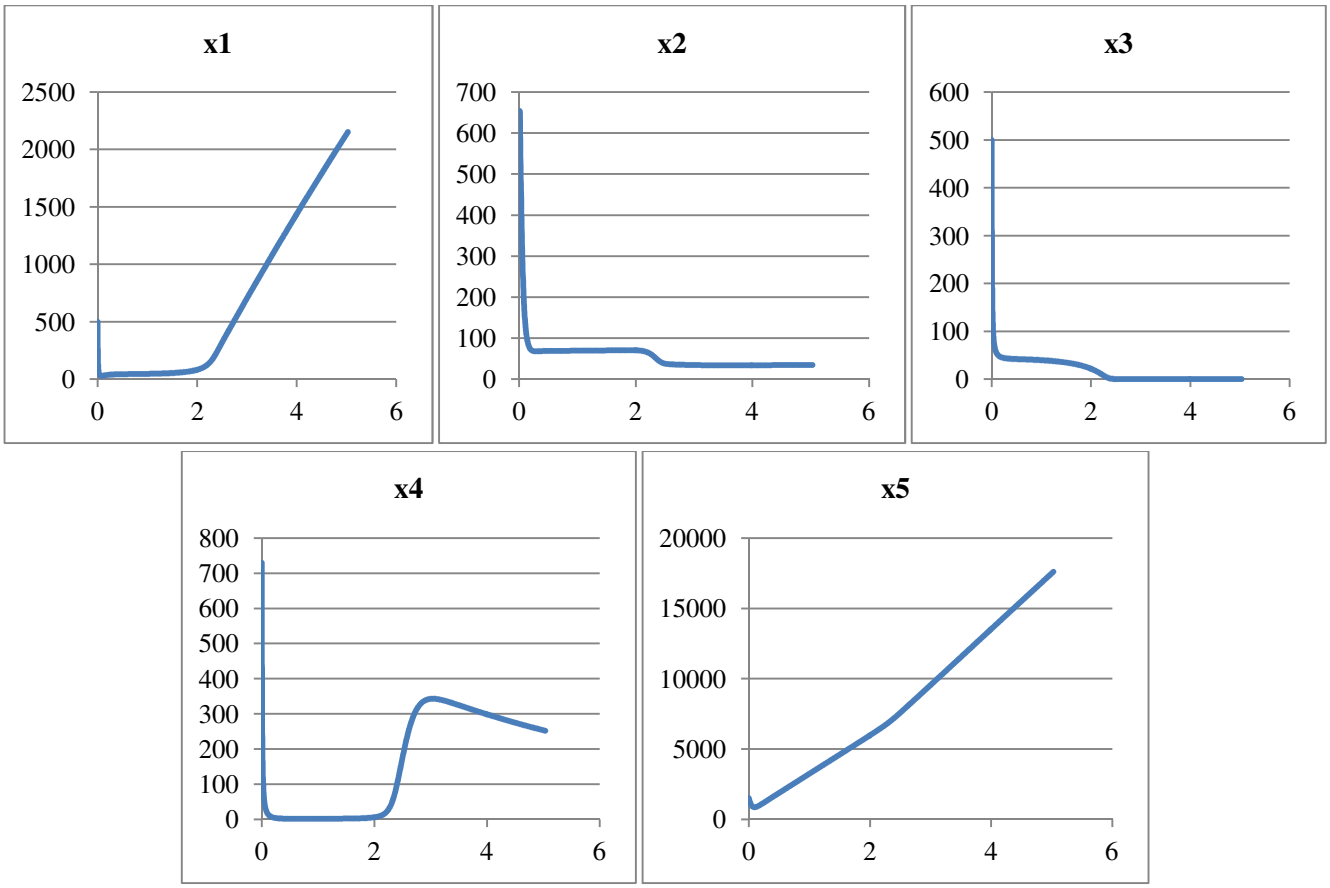
585 The AIDS patho-physiological parametric configuration of hypothetical patient #1 is denoted by P_1 and exhibited in
586 Table 1. A brief inspection of the data reveals explicitly that it is a non-equilibrium scenario. The simulation results show that
587 the HAART protocol impairs HIV-1 dynamics in this patient leading to eradication of plasma HIV-1 viremia. The simulation
588 results for patient #1 are exhibited in Figure 1. It can observed that the HIV-1 infected CD4+ T cells are eradicated in this
589 patient with the use of anti-AIDS pharmaco-therapeutic drug protocols. In addition, patient #1 experiences HAART- induced
590 immune system reconstitution as the uninfected CD4+ T cells and HIV-1 specific CD8+ T cells repopulate.

591

592 **Table 1 Parametric Configuration P_1**

TABLE I. Hypothetical AIDS Patient Parametric Configuration P_1

S_1 = 800 /day/μl a_1 = 0.15 /day/cell/μl b_1 = 0.019 /cell/μl α_1 = 0.5/day/virion/μl k_1 = 0.0005/day/μl q_1 = 0.00045/day/μl/cell e_{10} = 0.0025 cells/day/μl x_{10} = 500 cells/μl	S_2 = 800 /day/μl a_2 = 0.03 /day/cell/μl b_2 = 0.004/cell/μl α_2= 0.5/day/virion/μl k_2 = 0.005/day/μl q_2 = 0.00001/day/μl/cell β_1 = 1.05 virons/CD4$^+$/day K_1 = 0.0001/day/μl e_{20} = 0.005 cells/day/μl ξ_2 = 0.85 x_{20} = 400 cells/μl	S_3 = 10 /day/μl β_2 = 0.0015 virons/CD4$^+$/day/μl β_3 = 1.05 virons/CD4$^+$/day α_3 = 0.027 /day/virion/μl k_3 = 0.0001/day/μl e_{30} = 0.0001 /day η_1 = 0.25 ξ_3 = 0.001 x_{30} = 500 cells/μl	S_4 = 10 /day/μl a_4 = 0.35 /day/cell/μl b_4 = 0.01/cell/μl K_2 = 0.0024 /day/μl k_4 = 0.08/day/μl e_{40} = 0.0002 cells/day/μl η_2 = 0.45 x_{40} = 730 cells/μl	D = 5000 units σ_0 = 0.5 *mg*/day σ_2 = 30 *mg*/day σ_3 = 5 *mg*/day λ_0 = 5 *mg/L* λ_2 = 15 *mg/L* λ_3 = 0.025 *mg/L* x_{50} = 1500 cells/μl k_5 = 0.0 /day constant infusion



2

Figure 1 Simulation results using parametric configuration P_1

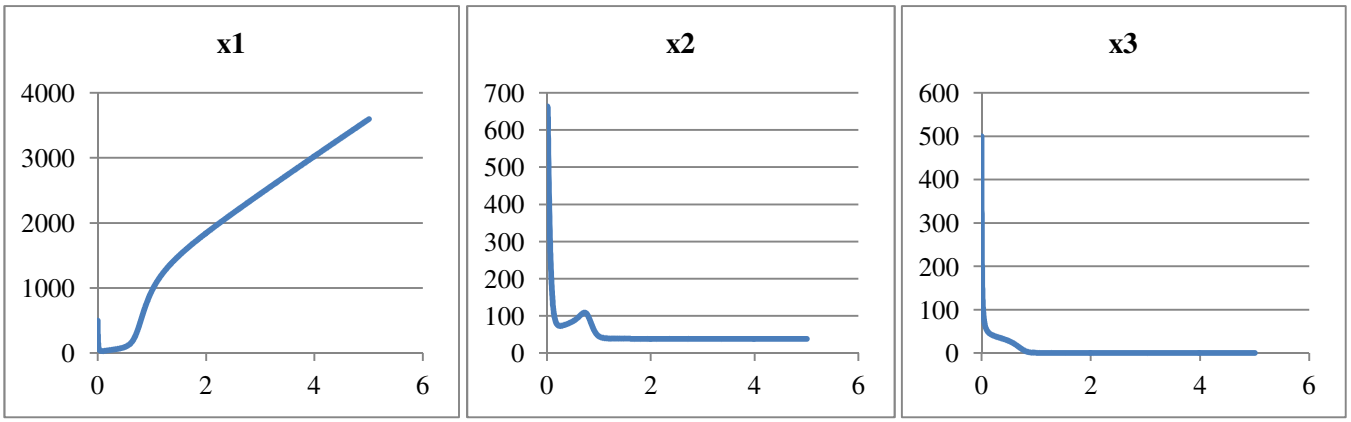
7.2 Simulation results for hypothetical AIDS patient #2

The hypothetical AIDS patient #2 is assigned the patho-physiological parameter configuration P_2 as presented in Table 2. As in the previous simulation, the configuration P2 does not depict an equilibrium configuration. The simulation results are exhibited in Figure 2. It can be observed that the this patient does have a clinically favorable prognosis under HAART treatment protocol. The AIDS patho - physiodynamics during the given HAART protocol is similar to that for patient #1, as the patient #2 also undergoes immune system reconstitution in which the CD4+ T cells repopulate. On the other hand, the proliferative activity of the HIV-1 specific CD8+ T cells appears to be down-regulated..

Table 2 Parametric Configuration P_2

TABLE 2. Hypothetical AIDS Patient Parametric Configuration P_2

$S_1 = 800$ /day/μl $a_1 = 0.15$ /day/cell/μl $b_1 = 0.005$ /cell/μl $\alpha_1 = 0.5$/day/virion/μl $k_1 = 0.0005$/day/μl $q_1 =$ 0.00045/day/μl/cell $e_{10} = 0.0025$ cells/day/μl $x_{10} = 500$ cells/μl	$S_2 = 800$ /day/μl $a_2 = 0.03$ /day/cell/μl $b_2 = 0.004$/cell/μl $\alpha_2 = 0.5$/day/virion/μl $k_2 = 0.005$/day/μl $q_2 =$ 0.00001/day/μl/cell $\beta_1 = 1.05$ virons/CD4$^+$/day $K_1 = 0.0001$/day/μl $e_{20} = 0.005$ cells/day/μl $\xi_2 = 0.85$ $x_{20} = 400$ cells/μl	$S_3 = 10$ /day/μl $\beta_2 = 0.0015$ virions/CD4$^+$/day/μl $\beta_3 = 1.05$ virons/CD4$^+$/day $\alpha_3 = 0.027$/day/virion/μl $k_3 = 0.0001$/day/μl $e_{30} = 0.0001$ /day $\eta_1 = 0.25$ $\xi_3 = 0.001$ $x_{30} = 500$ cells/μl	$S_4 = 10$ /day/μl $a_4 = 0.35$ /day/cell/μl $b_4 = 0.01$/cell/μl $K_2 = 0.0024$ /day/μl $k_4 = 0.08$/day/μl $e_{40} = 0.0002$ cells/day/μl $\eta_2 = 0.45$ $x_{40} = 730$ cells/μl	D = 5000 units $\sigma_0 = 0.5$ *mg*/day $\sigma_2 = 30$ *mg*/day $\sigma_3 = 5$ *mg*/day $\lambda_0 = 5$ *mg/L* $\lambda_2 = 15$ *mg/L* $\lambda_3 = 0.025$ *mg/L* $x_{50} = 1500$ cells/μl $k_5 = 0.0$ /day constant infusion



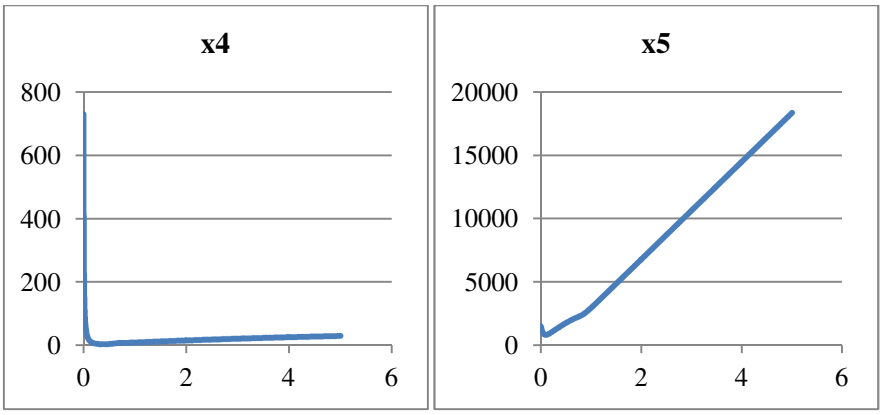


Figure 2 Simulation results using parametric configuration P_2

7.3 Simulation results for hypothetical AIDS patient #3

For this scenario, the patho-physiological parametric configuration of hypothetical patient #3 is as shown in Table 3. It must be noted that HIV-1 AIDS dynamics during HAART treatment protocol in this patient is exacerbated by contributions from latent reservoirs in contrast to the other hypothetical patients. The results of the simulation are shown in Figure 3. This is a non-equilibrium AIDS configuration simulation as it is evident parametric configuration and by the simulation time profile. The simulation results show that during the given HAART protocol, the hypothetical AIDS patient #3 experiences annihilation of uninfected CD4+ T cells and the HIV-1 specific CD8+ T cells . Consequently, immune system paralysis occurs as a consequence of the low CD4+ T cell number density, e leading to an exponential increase of the blood plasma HIV-1 viremia. This simulation represents an unfavorable AIDS outcome during HAART.

Table 3 Parametric Configuration P_3

TABLE 3. Hypothetical AIDS Patient Parametric Configuration P_3

S_1 = 800 /day/μl a_1 = 0.15 /day/cell/μl b_1 = 0.003 /cell/μl α_1 = 0.5/day/virion/μl k_1 = 0.0005/day/μl q_1 = 0.00045/day/μl/cell e_{10} = 0.0025 cells/day/μl x_{10} = 250 cells/μl	S_2 = 800 /day/μl a_2 = 0.03 /day/cell/μl b_2 = 0.004/cell/μl α_2= 0.5/day/virion/μl k_2 = 0.005/day/μl q_2 = 0.00001/day/μl/cell β_1 = 1.05 virons/CD4$^+$/day K_1 = 0.0001/day/μl e_{20} = 0.005 cells/day/μl ξ_2 = 0.85 x_{20} = 400 cells/μl	S_3 = 10 /day/μl β_2 = 0.0015 virions/CD4$^+$/day/μl β_3 = 1.05 virons/CD4$^+$/day α_3 = 0.027/day/virion/μl k_3 = 0.0001/day/μl e_{30} = 0.0001 /day η_1 = 0.25 ξ_3 = 0.001 x_{30} = 500 cells/μl	S_4 = 10 /day/μl a_4 = 0.35 /day/cell/μl b_4 = 0.002/cell/μl K_2 = 0.095 /day/μl k_4 = 0.08/day/μl e_{40} = 0.0002 cells/day/μl η_2 = 0.45 x_{40} = 730 cells/μl	D = 5000 units σ_0 = 1.0 *mg*/day σ_2 = 30 *mg*/day σ_3 = 5 *mg*/day λ_0 = 5 *mg/L* λ_2 = 15 *mg/L* λ_3 = 0.025 *mg/L* x_{50} = 3000 cells/μl k_5 = 0.0 /day Constant Infusion

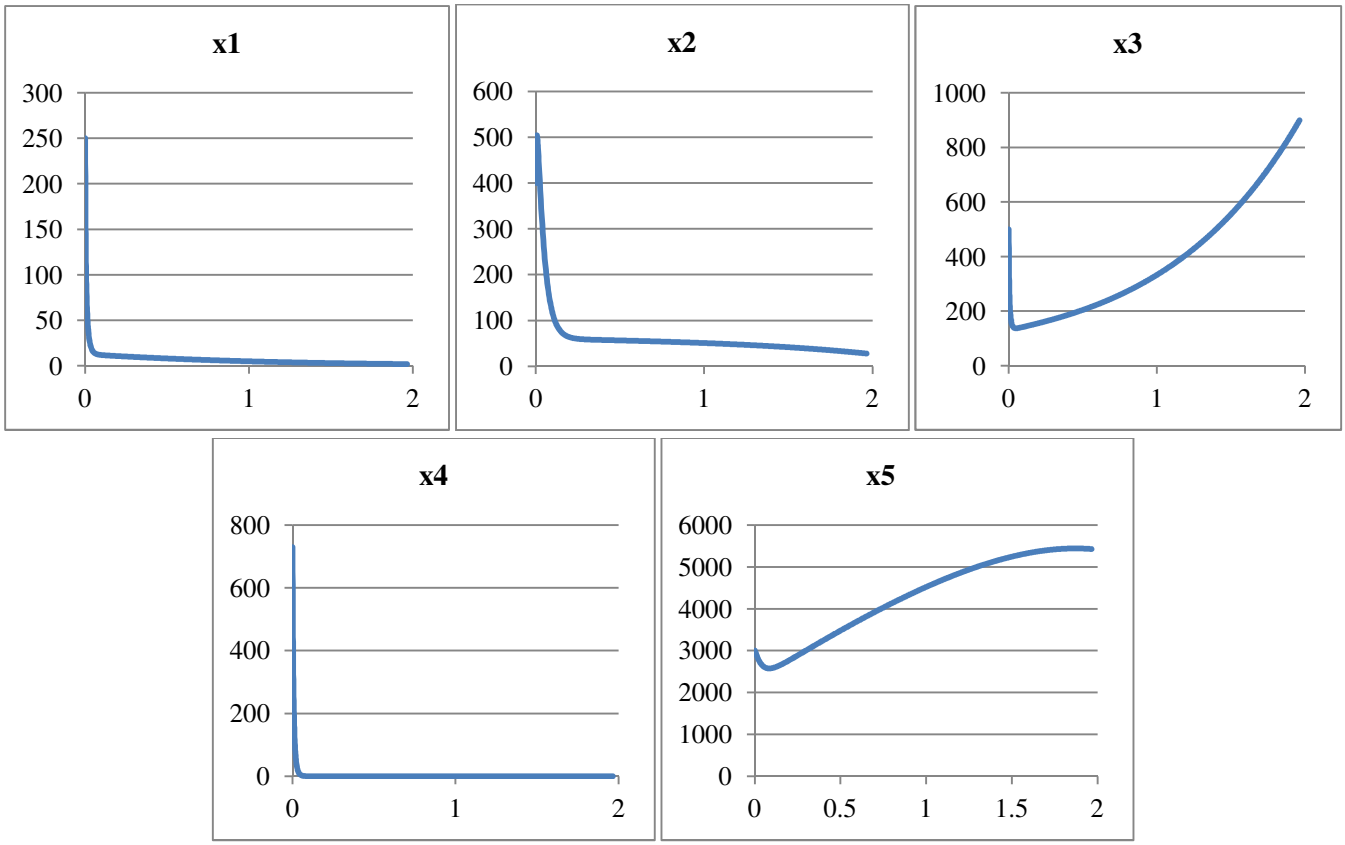


Figure 3 Simulation results using parametric configuration P_3

8. Summary, Discussion and Future Work

The current paper is elaborate and quantitative attempt to construct medically applicable mathematic models and derive criteria for efficacious HAART protocol for an AIDS patient. The mathematical equations presented in Section 3 are a generalization of the models by Wodarz and Nowak [16], Perelson et al[13], Tang et al. [15], and many other authors by incorporating more clinically relevant parameters of HIV-1 patho-physiodynamics. In particular, interleukim-2 activation of both CD_4+ T cells and CD_8+ T cells are implicitly incorporated into the model. In this paper, it has been demonstrated that the parameters (a_1, b_1) and (a_4, b_4) play a significant role in determining the efficacious outcomes of HAART. Clearly, the clinically desirable outcomes are the rest points E4 and E3. The criteria for the existence of E4 and E3 are listed respectively in Theorem 5.1, and Theorem 5.4. These theorems give the conditions under which both E4 and E3 can be temporarily or transiently attained. The criteria for E4 and E3 to become global attractors are listed Theorem 6.1 and Theorem 6.2. These theorems, expressed in terms of simple clinically attainable and measurable parameters, give the sufficient conditions for the

cure of AIDS. It will be emphasized that there exist other therapeutic criteria but these are intractable and extremely arduous to achieve in a clinical setting.

One essential feature of this research is that the HAART protocol is implemented by using the constant continuous intravenous infusion or constant continuous transdermal infusion of the drug. As such, the criteria derived in this paper are applies to these settings. The mathematical model for intermittent caplet or matrix tablet per oral drug administration can be derived using the non-autonomous version of the model equations involving the drug input function $f(t)$ discussed by Nani and Jin in [10].

The scenarios for clinical failure during HAART due to extreme drug toxicity are represented by the rest points E1 and E5.The criteria for these therapeutic outcomes are described by Theorem 5.3 and Theorem 5.2, respectively.

The future work will involve the construction of mathematical models which will describe an AIDS therapy using HAART in addition to ACI (Active Cellular Immunotherapy) involving interleukim-2. Also, in the future, the mathematical model for HAART will include the roles of mutations such as the delta32 CCR5 on therapeutic outcomes.

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